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ORIGINAL ARTICLE

Estimating the risk of complications related to re-exploration for bleeding after adult cardiac surgery: a systematic review and meta-analysis

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Abstract

OBJECTIVE: The aim of this study was to evaluate the impact of re-exploration for bleeding after cardiac surgery on the immediate postoperative outcome.

METHODS: Systematic review of the literature and meta-analysis of data on re-exploration for bleeding after adult cardiac surgery were performed.

RESULTS: The literature search yielded eight observational studies reporting on 557 923 patients and were included in the present analysis. Patients requiring re-exploration were significantly older, more frequently males, had a higher prevalence of peripheral vascular disease and preoperative exposure to aspirin, and more frequently underwent urgent/emergency surgery. Re-exploration was associated with significantly increased risk ratio (RR) of immediate postoperative mortality (RR 3.27, 95% confidence interval (CI) 2.44–4.37), stroke, need of intra-aortic balloon pump, acute renal failure, sternal wound infection, and prolonged mechanical ventilation. The pooled analysis of four studies (two being propensity score-matched pairs analysis) reporting adjusted risk for mortality led to an RR of 2.56 (95%CI 1.46–4.50). Studies published during the last decade tended to report a higher risk of re-exploration-related mortality (RR 4.30, 95%CI 3.09–5.97) than those published in the 1990s (RR 2.75, 95%CI 2.06–3.66).

CONCLUSIONS: This study suggests that re-exploration for bleeding after cardiac surgery carries a significantly increased risk of postoperative mortality and morbidity.

Keywords: Cardiac surgery • Bleeding • Resternotomy • Re-exploration

INTRODUCTION

Prevention and treatment of excessive bleeding after cardiac surgery are of major concern among cardiac surgeons and anesthesiologists as its treatment is associated with the risks related to exposure to allogeneic blood and with significant use of hospital resources. The risk of significant bleeding is particularly increased by the currently widespread preoperative exposure to potent anti-platelet drugs [1], and likely it will further increase in view of the concerns regarding safety of antifibrinolytics [2]. In this scenario, re-exploration after cardiac surgery is the most feared bleeding-related complication, as it is associated with significant mortality and morbidity [3,4]. However, evidence regarding the negative prognostic impact of re-operation for bleeding may be flawed by the higher baseline operative risk of these patients [5].

The present study aimed to estimate the prognostic impact of re-exploration for bleeding after cardiac surgery and to evaluate whether it is an independent risk factor for adverse outcome.

MATERIAL AND METHODS

This meta-analysis was performed in accordance with the Cochrane Handbook for Systematic Reviews [6]. An English-language literature review was performed through PubMed, Scopus, Science Direct, and Cochrane Library up to January 2011 for any study evaluating the outcome after re-operation for bleeding after adult cardiac surgery. The words employed in the search were: ‘reoperation’, ‘re-exploration’, ‘resternotomy’, and ‘bleeding’ combined with ‘coronary artery bypass’, ‘coronary bypass’, ‘myocardial revascularization’, ‘aortic valve', 'mitral valve', 'ascending aorta', and 'cardiac surgery'. Reference lists of obtained articles were searched as well.

This study was not financially supported.

Inclusion criteria

Both prospective and retrospective observational studies published in English language as full-length articles and reporting on the outcome of patients who underwent re-exploration for bleeding after adult cardiac surgery were considered for this analysis. Studies including re-exploration for causes other than major postoperative bleeding were excluded and we restricted this analysis to studies published after year 1980 to avoid any major bias in terms of medical and surgical-treatment approaches. The language of the articles was defined as reported in PubMed and Scopus. We did not include in this study unpublished data or data reported only in abstract. We applied the guidelines for Meta-analysis of Observational Studies in Epidemiology (MOOSE) [7].

Data collection and assessment of data quality

One investigator (FB) identified the articles potentially dealing with this topic. Four investigators (FB, JL, JH, and RM) independently abstracted data from all eligible studies using a standardized Excel file. These authors retrieved data on study design, study size, patient demographics, type of intervention, and 30-day/in-hospital outcome. Data were retrieved only from the articles, and no attempt was made to get missing data from the authors. Any disagreement was solved by consensus.

The quality of observational, cohort studies was assessed by use of Newcastle–Ottawa scale, which is a nine-point scale that assigns points on the basis of the process of selection (0–4 points), comparability (0–2 points), and identification of the outcomes of study participants (0–3 points) in cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

Outcomes of interest

The main outcome end point of this study was immediate postoperative mortality defined as any death occurring during in-hospital stay or 30-day postoperative period. Secondary outcome end points were sternal wound infection, stroke, acute renal failure, need of intra-aortic balloon pump, and prolonged mechanical ventilation. Sternal wound infection was defined as any deep wound infection or mediastinitis. Acute renal failure was defined as an increase in postoperative serum concentration of creatinine >200 μmol l^{-1} or need of dialysis. Prolonged mechanical ventilation and stroke were reported, as originally defined by the authors.

Statistical analysis

Statistical analysis was performed using Review Manager 5.0.18 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) [7]. Differences in continuous variables were reported as mean differences with 95% confidence interval (95%CI). Differences in preoperative and outcome dichotomous variables were reported as risk difference (RD) with 95%CI. The pooled risk of adverse event was expressed as risk ratio (RR) with 95%CI. The natural logarithm of adjusted odds ratio (OR) and the estimated standard error of each study were entered in to Review Manager to estimate pooled adjusted OR for in-hospital mortality by generic inverse variance analysis. Standard error of each retrieved adjusted OR was estimated by the following formula: ln SE = (ln of upper confidence limit − ln of lower confidence limit)/3.92. Generic inverse variance analysis was first done for adjusted ORs obtained only from multivariate analysis and then by also including unadjusted ORs estimated from propensity score- matched pairs. Heterogeneity has been assessed by using the I^2 statistic. $I^2 < 40\%$ was considered as non-important heterogeneity. In case of important heterogeneity, we used the random-effects analysis; otherwise, we used fixed-effect analysis. In this study, we did not perform meta-regression analysis because of the small number of studies herein included. Instead, sensitivity analysis was performed according to the type of surgery, mid-date of studies, and timing of re-exploration. A $P < 0.05$ was considered statistically significant.

RESULTS

Literature search

The literature search performed in January 2011 yielded 417 articles, of which 15 were found to be pertinent with this topic. After full article review, seven articles were excluded because no data regarding re-exploration for bleeding after cardiac surgery and related complications were available. Eight articles [3–5, 8–12] were found to report data of interest and fulfilled the inclusion criteria of the present study. Table 1 summarizes the main characteristics of these studies, the amount of isolated coronary artery bypass grafting procedures performed, the rate of re-exploration for major bleeding, and proportions of major immediate complications. Table 2 summarizes data quality, as assessed by the Ottawa–Newcastle scale. Two out of seven studies [3,4] reported only the results of propensity score-matched pairs' analysis.

Predictors of re-exploration for bleeding

The decision to perform re-exploration was made according to varying criteria, but, in all of studies, re-operation was carried out for severe postoperative bleeding and/or cardiac tamponade. Table 3 summarizes the differences in clinical and operative characteristics of patients, according to the need of re-exploration for bleeding after cardiac surgery. Patients requiring re-exploration were older, more frequently male, had more often peripheral vascular disease and preoperative exposure to aspirin, and more frequently underwent urgent/emergency surgery. However, data on these variables were not reported in all studies and, thus, this analysis may be biased. Furthermore, no data regarding the timing of exposure to aspirin were available and data regarding other anti-thrombotic agents were scanty for specific analysis. Anyway, among these risk factors, a risk difference of 9% (95%CI 2–19%) in terms of urgent/emergency surgery was observed among 538 553 patients reported in six studies. Besides its well-recognized impact on postoperative mortality, an increased incidence of resternotomy for bleeding

Table 1: Characteristics of observational studies included in this meta-analysis on the impact of re-exploration for excessive bleeding after cardiac surgery. Proportions of adverse events are reported for patients who underwent re-exploration versus control patients, respectively

Study	Country	Study design	Study period	Number of patients	Isolated CABG (%)	Re-exploration for bleeding (%)	Immediatemortality (%)	Sternal wound infection (%)	Need of IABP (%)	Acute renal failure (%)	Stroke (%)	Prolonged mechanical ventilation (%)
Unsworth-White 1995	UK	P	1992–1993	2221	70.4	3.8	22.4 versus 5.5	-	14.1 versus 3.1	9.4 versus 3.3	-	14.1 versus 3.1
Moulton 1996	USA	R	1986–1993	6015	68.6	4.2	10.7 versus 4.2	2.4 versus 0.9	-	15.8 versus 3.8	3.6 versus 1.9	24.5 versus 8.6
Sellman 1997	Sweden	R	1970–1994	8563	80.5	4.4	5.8 versus 3.0	1.9 versus 1.0	-	-	-	-
Dacey 1998	USA	P	1992–1995	8586	100	3.6	9.5 versus 3.3	-	-	-	-	-
Karthik 2004	UK	P	1999–2002	168	100	PSA	1.2 versus 3.4	9.5 versus 4.8	8.3 versus 2.4	9.5 versus 2.4	6.0 versus 3.6	32.1 versus 7.1
Choong 2007	UK	P	2003–2005	3220	81.9	5.9	11.0 versus 2.2	-	26.2 versus 6.1	4.2 versus 0.8	-	-
Ranucci 2008	Italy	R	2001–2007	464	39.7	PSA	14.2 versus 3.4	-	10.8 versus 3.0	17.7 versus 6.9	0.9 versus 0	4.7 versus 3.0
Mehta 2009	USA	P	2004–2007	528 686	100	2.4	9.6 versus 2.2	1.7 versus 0.3	19.2 versus 9.8	-	2.6 versus 1.2	42.4 versus 9.3

P: prospective study; R: retrospective study; PSA: propensity score analysis, only matched pairs reported; CABG: coronary artery bypass grafting.

after urgent/emergency operation suggests that these patients were more likely exposed preoperatively to anti-platelet/anti-coagulant agents.

Sources of excessive bleeding

Table 4 summarizes the pooled proportions of source of bleeding, as reported in three studies [8,10,11]. Diffuse bleeding (diffuse ooze, no surgical cause identified) was found at re-exploration in 20.6% (95%CI 13.6–29.9%) of cases. It was not possible to evaluate the impact of the nature of bleeding on the postoperative outcome.

Re-exploration and postoperative morbidity and mortality

Re-exploration for bleeding was associated with significantly increased risk of immediate postoperative mortality (Fig. 1), stroke, need of intra-aortic balloon pump, acute renal failure, sternal wound infection, and prolonged mechanical ventilation, as summarized in Table 5. The negative prognostic impact of re-exploration on immediate postoperative mortality was consistent in all studies, but the smallest one (Fig. 1).

Four studies [3,4,8,9] reported on adjusted ORs of the impact of re-exploration for bleeding on the immediate postoperative mortality. The pooled RR of these studies was 2.56 (95%CI 1.46–4.50, I^2 = 55%, random effect analysis, P = 0.001) (Fig. 2). ORs were extracted in two of these studies from propensity matched pairs' analysis [3,4]. When only adjusted ORs obtained from multivariate analysis were included in the analysis [8,9], the pooled RR for immediate postoperative mortality was 2.35 (95% 1.62–3.38, I^2 = 7%, fixed-effect analysis, P < 0.00001).

The increased risk of stroke after re-exploration was another observation of particular concern (RR 2.18, 95%CI 1.96, 2.43). This finding was consistent across all studies, but no data were available to assess whether re-exploration was an independent risk factor for cerebrovascular complications.

Sensitivity analysis

Two studies [3,8] reported on the mortality rates after re-exploration for bleeding performed within 12 h or later. Re-exploration for bleeding performed > 12 h after surgery was associated with a significantly increased risk of mortality (21.5% vs 5.1%: 14/65 vs 11/215 patients) (RR 5.22, 95%CI 2.43–11.21, I^2 = 0%, fixed-effect analysis, P < 0.00001; RD 18%, 95%CI 8–29%, I^2 = 2%, fixed-effect analysis, P = 0.0007).

Analysis of studies including only patients, who underwent isolated coronary artery bypass surgery [3,5,12], showed a significant higher risk of postoperative mortality among patients, who underwent re-exploration for bleeding (RR 3.23, 95%CI 1.88–5.55, I^2 = 81%, random-effect analysis, P < 0.00001). Pooled analysis of studies including procedures other than isolated coronary artery bypass operations [4,9,10] also showed a higher risk of mortality (RR 3.24, 95%CI 2.25–4.65, I^2 = 67%, random-effect analysis, P < 0.00001).

Studies published during the last decade [3–5,8] had a higher pooled RR for mortality (RR 4.30, 95%CI 3.09–5.97, I^2 = 44%,

Table 2: Newcastle–Ottawa quality assessment of observational studies included in this meta-analysis on the impact of re-exploration for bleeding after cardiac surgery

Study	Representativeness	Selection	Ascertainment of exposure	Outcome not comparability present at start of study	Comparability	Assessment of outcome	Follow-up long enough	Adequacy of follow-up
Unsworth-White 1995	★	★	★	★		★	★	★
Moulton 1996	★	★	★	★		★	★	★
Sellman 1997	★	★	★	★		★	★	★
Dacey 1998	★	★	★	★		★	★	★
Karthik 2004	★	★	★	★	★★	★	★	★
Choong 2007	★	★	★	★		★	★	★
Ranucci 2008	★	★	★	★	★★	★	★	★
Mehta 2009	★	★	★	★		★	★	★

Table 3: Pooled clinical variables and operative data of patients who underwent or not re-exploration for bleeding after cardiac surgery*

Variable	Number of patients/number of studies	Risk difference (95%CI)/mean difference	Analysis model	P–value
Age (years)	12088/5	−2.19 (−3.03, −1.35)	FE	<0.00001
Female	557923/8	0.02 (0.01, 0.03)	FE	<0.00001
Peripheral vascular disease	537440/3	−0.02 (−0.03, −0.02)	FE	<0.00001
Renal failure	543455/4	−0.02 (−0.04, 0.00)	RE	0.08
Pulmonary disease	547139/6	−0.01 (−0.03, 0.01)	RE	0.34
Diabetes	547139/6	0.00 (−0.03, 0.03)	RE	0.78
Redo cardiac surgery	557923/8	0.00 (−0.02, 0.02)	RE	0.85
Emergent/urgent operation	547139/6	−0.09 (−0.16, −0.02)	RE	0.01
Exposure to aspirin	537921/3	−0.02 (−0.03, −0.01)	FE	<0.00001
CPB time	6249/2	−12.96 (−34.17, 8.26)	RE	0.23

FE: fixed effect; RE: random effect; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass. *: negative values are in favour of no reexploration for bleeding.

random-effect analysis, $P < 0.00001$) than those published in the 1990s [9–12] (2.75, 95%CI 2.06–3.66, I^2 = 52%, random-effect analysis, $P < 0.00001$).

DISCUSSION

The present analysis provides evidence that excessive bleeding requiring re-exploration is associated with increased morbidity and mortality after adult cardiac surgery. Such results are derived from observational, mostly retrospective studies, and thus possibly biased; but, otherwise, their quality seems to be satisfactory (Table 1). The results are consistent along the studies and outcome end points. Only one study reported lower mortality rate after re-exploration for excessive bleeding compared with controls [3]; but this study was of relatively small size and was not powered enough to reliably detect differences in terms of mortality. However, the evaluation of all other major outcome end points showed unfavourable results associated with re-exploration [3].

The mechanisms behind the poor outcome after re-operation for excessive bleeding are likely multifactorial. The patients requiring re-exploration have multiple, preoperative, high-risk

Table 4: Pooled proportions of sources of bleeding found in patients who underwent re-exploration for bleeding after cardiac surgery [8,10,11].

Source of bleeding	Pooled proportions	Analysis model	P-value
Internal mammary artery branches	22.7% (11.2%, 40.7%)	RE	<0.0001
Vein graft branches	7.9% (6.0%, 10.2%)	RE	0.457
Anastomoses	16.9% (13.9%, 20.3%)	RE	0.24
Other sites	30.0% (19.7%, 42.7%)	RE	<0.0001
Diffuse bleeding	20.6% (13.6%, 29.9%)	RE	0.003

RE: random effect.

features and their operation is more often performed on urgent/emergency basis, which certainly contribute to the major bleeding complications. Despite these considerations, in two studies [8,9], re-exploration for bleeding remained as an independent

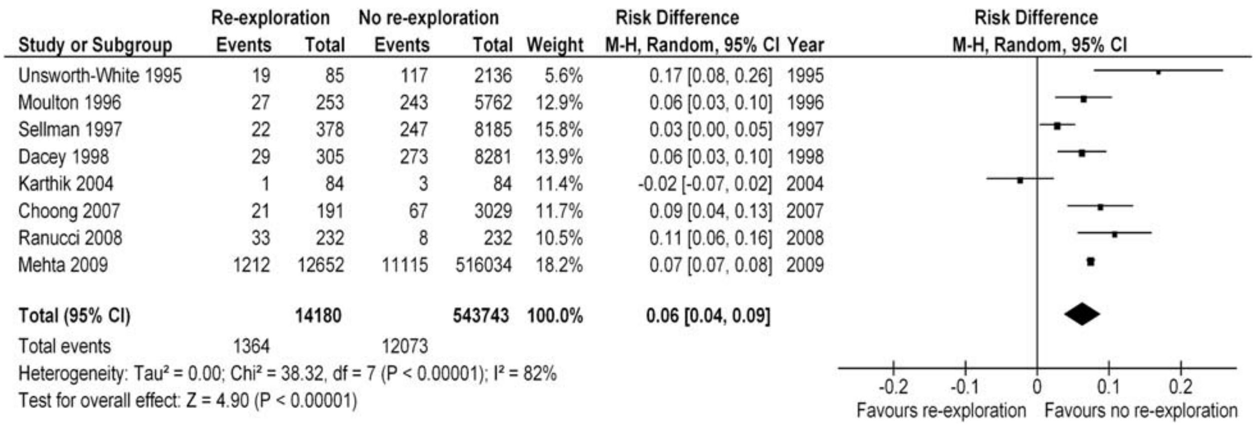

Figure 1: Forest plot showing the pooled risk ratio for immediate postoperative mortality after re-exploration for bleeding after cardiac surgery.

Table 5: Risk ratios and risk differences of immediate mortality and morbidity after cardiac surgery in patients with versus those without need of re-exploration for bleeding

Outcome end-point	Number of patients/number of studies	Risk ratio (95%CI)	Risk difference (95%CI)	Analysis model	*P*-value
Mortality	557923/8	3.27 (2.44, 4.37)	0.06 (0.04, 0.09)	RE	<0.00001
Sternal wound infection	5426877/4	4.52 (3.95, 5.18)	0.01 (0.01, 0.02)	FE	<0.00001
Need of IABP	534759/5	3.34 (1.95, 5.72)	0.11 (0.07, 0.14)	RE	<0.00001
Acute renal failure	12088/5	3.70 (2.91, 4.69)	0.08 (0.03, 0.12)	RE	<0.00001
Stroke	535333/4	2.18 (1.96, 2.43)	0.01 (0.01, 0.02)	FE	<0.00001
Prolonged mechanical ventilation	535333/4	3.39 (2.28, 5.05)	0.19 (0.00, 0.38)	RE	<0.00001

FE: fixed effect; RE: random effect; IABP: intra-aortic balloon pump.

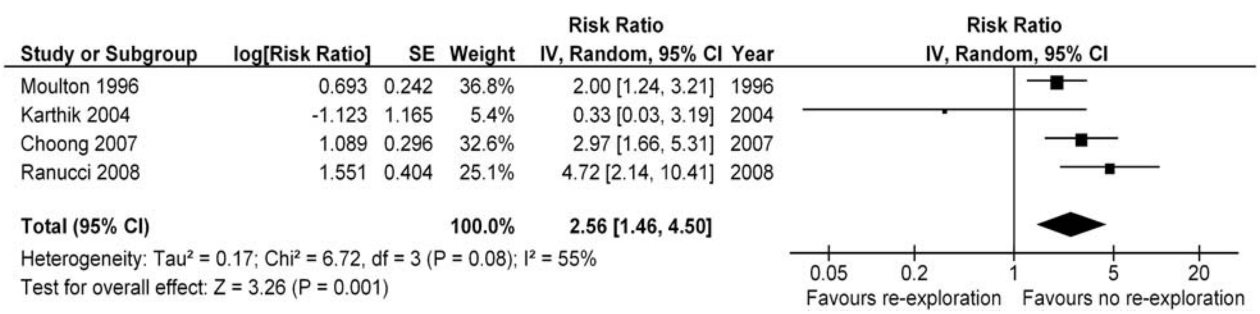

Figure 2: Forest plot showing the pooled risk ratio of studies reporting adjusted odds ratios for immediate postoperative mortality after re-exploration for bleeding after cardiac surgery.

predictor of immediate postoperative mortality at logistic regression. Two further studies [3,4] reported the results of propensity score-matched pairs' analysis, and, thus, they were valuable to estimate the prognosis in patient populations with similar operative risk. The pooled RR of adjusted ORs reported in these studies (Fig. 2) provides clear evidence that re-exploration for bleeding has independent negative impact on postoperative mortality. Furthermore, Moulton et al. [9] showed an increased mortality risk after re-exploration for bleeding also in low-risk patients (4.8% vs 1.2%, adjusted OR 4.4, P = 0.03). Mortality risk seems also to increase with increasing amount of red blood cell units transfused in both re-exploration and control patients [4,9], thus providing a further indirect evidence of the prognostic impact of severe bleeding.

The quality of the data on preoperative anti-thrombotic treatment was suboptimal, and studies encompass a rather long period during which anti-platelet/anticoagulation strategies have markedly changed and became more and more aggressive. More importantly, we were not able to retrieve sufficient data on pre, intra- and postoperative anti-thrombotic medication, and this may represent a serious limitation in the interpretation of these data. Thus, it is not clear whether cardiac, pulmonary, renal, and cerebrovascular complications were mostly related to the severity of postoperative as well as intra-operative bleeding, to the preoperative operative risk profile of the patient, to suboptimal surgical treatment or to technical complications.

Importantly, pooled analysis of two studies [3,8] showed a marked increased mortality (RD 18%) in patients undergoing re-exploration > 12 h after surgery. Such a markedly increased risk probably cannot be explained by the increased blood loss and/or amount of red blood cells' unit transfusions [4,8]. We can speculate that, despite a similar blood loss and extent of pericardial hematoma, patients undergoing late resternotomy might have more compromised baseline or postoperative cardiac function, which made bleeding and cardiac tamponade less 'tolerable'. However, the available data suggest that late re-exploration may contribute to most of re-exploration-related deaths and this should be carried as soon as excessive bleeding and/or cardiac tamponade-related hemodynamic instability becomes evident.

The present findings should be viewed as a background for further studies, as re-exploration for excessive bleeding revealed itself an important and preventable complication, with potential for significant improvement of the outcome of adult cardiac surgery and for marked saving of hospital resources. We believe that future research on this topic should focus on:

- risk of re-exploration for bleeding and related outcome according to different types of cardiac procedures;
- prognostic impact of 'surgical' versus diffuse 'non-surgical' source of bleeding at re-exploration;
- prognostic impact of timing of re-exploration focusing also on pre- and postoperative cardiac function;
- prognostic impact of re-exploration for bleeding on stroke;
- evaluation of long-term outcome after re-exploration for bleeding; and
- propensity score analysis: the use of propensity score matching, stratification as well as regression adjustment are advised for an adequate adjustment of baseline and operative variables [13], particularly for an appropriate evaluation of the results of observational series.

In conclusion, despite the limitations related to the nature of the studies included in this meta-analysis, re-exploration for bleeding after cardiac surgery seems to carry a significantly increased risk of immediate postoperative mortality and morbidity. In view of these findings, any effort to avoid excessive bleeding requiring re-exploration may lead to marked improvement of the outcome after adult cardiac surgery.

Conflict of interest: none declared.

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